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Cancer Research

Clinical Cancer Research

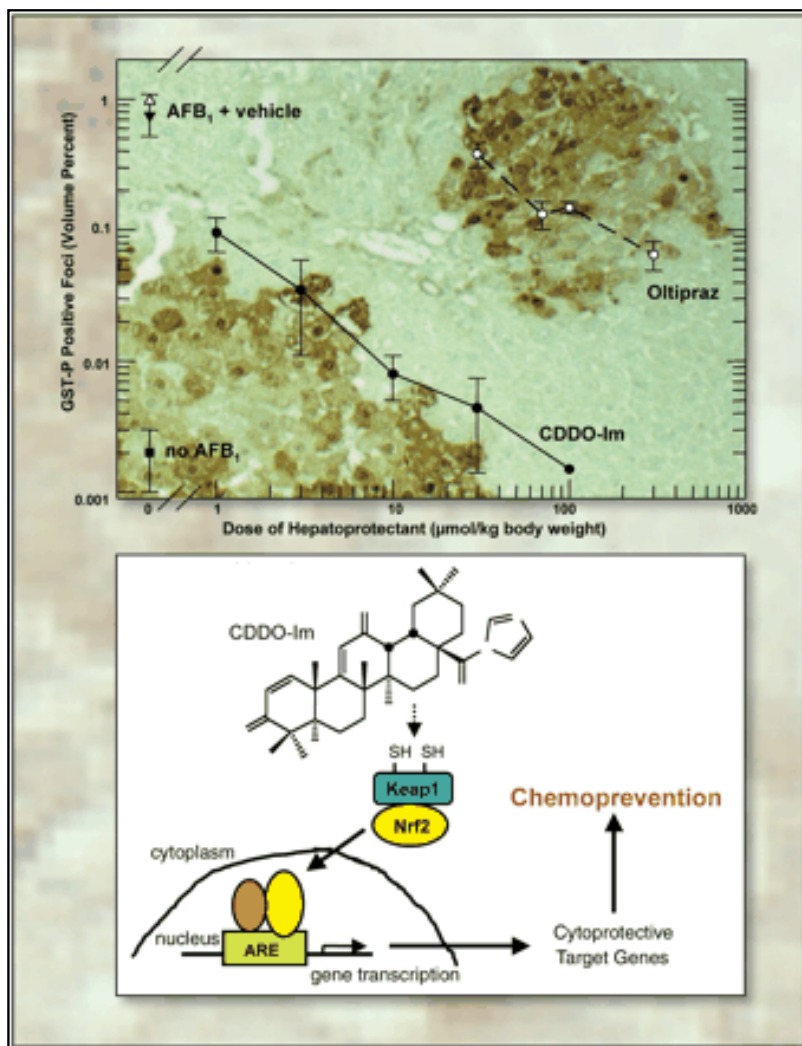
Cancer Epidemiology Biomarkers & Prevention

Molecular Cancer Therapeutics

Molecular Cancer Research

Cell Growth & Differentiation

About the Cover



On the Cover:

Synthetic triterpenoids are potent inducers of phase 2 enzymes *in vitro* as well as inhibitors of inflammation *in vivo*. These properties make triterpenoids attractive candidates for cancer chemoprevention, prompting Yates et al., to evaluate one of the most potent triterpenoids, CDDO-Im, as a chemopreventive agent against aflatoxin-induced tumorigenesis in rats. CDDO-Im engendered an 85% reduction in the hepatic focal burden of preneoplastic lesions (glutathione S-transferase P positive foci) when administered at 1 more potent than oltipraz, an established modulator of aflatoxin metabolism in humans, in this rat antitumorigenesis model (top panel). The graph is superimposed onto an image of two GST-P positive foci (photograph taken by Dr. Vince Memoli, Dartmouth-Hitchcock Medical Center, Lebanon, NH). The two GST-P⁺ cytoprotective genes in manner dependent upon the transcription factor Nrf2. The

bottom panel shows the proposed pathway for induction of Nrf2-regulated cytoprotective genes by CDDO-Im. The unparalleled in vivo potency of CDDO-Im highlights the chemopreventive promise of targeting the Nrf2 signaling pathway with triterpenoids.

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Epidemiology and Prevention

Potent Protection against Aflatoxin-Induced Tumorigenesis through Induction of Nrf2-Regulated Pathways by the Triterpenoid 1-[2-Cyano-3-,12-Dioxooleana-1,9(11)-Dien-28-Oyl]Imidazole

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Synthetic triterpenoid analogues of oleanolic acid are potent inducers of the phase 2 response as well as inhibitors of inflammation. We show that the triterpenoid, 1-[2-cyano-3-,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im), is a highly potent chemopreventive agent that inhibits aflatoxin-induced tumorigenesis in rat liver. The chemopreventive potency of CDDO-Im was evaluated by measuring inhibition of formation of putative preneoplastic lesions (glutathione *S*-transferase P positive foci) in the liver of rats exposed to aflatoxin B₁. CDDO-Im produces an 85% reduction in the hepatic focal burden of preneoplastic lesions at 1 μmol/kg body weight and a >99% reduction at 100 μmol/kg body weight. CDDO-Im treatment reduces levels of aflatoxin-DNA adducts by ~40% to 90% over the range of 1 to 100 μmol/kg body weight. Additionally, changes in mRNA levels of genes involved in aflatoxin metabolism were measured in rat liver following a single dose of CDDO-Im. *GSTA2*, *GSTA5*, *AFAR*, and *EPHX1* transcripts are elevated 6 hours following a 1 μmol/kg body weight dose of CDDO-Im. Microarray analysis using wild-

type and *Nrf2* knockout mice confirms that many phase 2 and antioxidant genes are induced in an Nrf2-dependent manner in mouse liver following treatment with CDDO-Im. Thus, low-micromole doses of CDDO-Im induce cytoprotective genes, inhibit DNA adduct formation, and dramatically block hepatic tumorigenesis. As a point of reference, oltipraz, an established modulator of aflatoxin metabolism in humans, is 100-fold weaker than CDDO-Im in this rat antitumorigenesis model. The unparalleled potency of CDDO-Im *in vivo* highlights the chemopreventive promise of targeting Nrf2 pathways with triterpenoids. (Cancer Res 2006; 66(4): 2488-94)

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